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Preliminary Results of Phase I/II Study of High-Dose-Rate Intraoperative Radiation Therapy for Pediatric Tumors

MICHAEL J. ZELEFSKY, MD, MICHAEL P. LaQUAGLIA, MD, FERESHTEH GHAVIMI, MD, JOANNE BASS, MPH, AND LOUIS B. HARRISON, MD
From the Brachytherapy Service, Department of Radiation Oncology (M.J.Z., J.B., L.B.H.), Pediatric Surgery Service, Department of Surgery (M.P.L.), and the Department of Pediatrics (F.G.), Memorial Sloan Kettering Cancer Center, New York, NY

Ten children with locally advanced or recurrent tumors were treated on a Phase I/II study to assess the feasibility and toxicity of intraoperative radiotherapy (IORT) for primary and recurrent pediatric solid malignancies at high risk for local recurrence. Eligible patients include all primary and recurrent pediatric solid tumors that are amenable to resection and have residual microscopic or gross disease after surgery. In all cases, after a gross tumor resection was performed, a flexible, transparent, multichannel applicator was placed and secured within the tumor bed. Once the position of the applicator was optimized, the applicator catheters were attached to the cables of a high-dose-rate remote afterloader, and 1,200 cGy prescribed to 0.5–1.0 cm from the applicator was delivered to the tumor bed via the remote afterloader.

One patient with a malignant teratoma developed a peri-rectal abscess 1 month after treatment; no other complications were noted. The 2-year actuarial local recurrence-free and distant metastases-free survival were 80% and 59%, respectively, with a median follow-up of 12 months (range: 3–18 months).

The preliminary results suggest that high-dose-rate IORT is a safe and feasible modality for pediatric tumors at high risk for local recurrence. Longer follow-up will be needed to assess fully the toxicity and efficacy of this approach.

KEY WORDS: **intraoperative radiotherapy, pediatric tumors, high-dose-rate, brachytherapy**

INTRODUCTION

Recurrent or persistent disease after standard therapeutic interventions for pediatric tumors represents a formidable challenge for the oncologist. In general, such tumors are not as responsive to second-line chemotherapeutic agents, and further surgery to encompass all disease would often entail extensive, radical procedures. For local radiotherapy to be effective in this setting, high doses would be necessary, which often exceed the tolerance of growing normal tissue structures. Given the obvious concerns of long-term effects of treatment in the pediatric patient population, efforts to reduce radiation dose to normal tissues while maximizing the dose to tumor are essential. Such efforts may not only potentially enhance local control, but may minimize treatment-related complications and the risk of developing second malignancies. In addition, especially in the setting of recurrent or persistent disease, shorter courses of radiotherapy may be advantageous in order to allow more rapid integration of systemic therapies.

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Address reprint requests to Michael J. Zelefsky, M.D., Memorial Sloan Kettering Cancer Center, Department of Radiation Oncology, 1275 York Avenue, New York, New York 10021.

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In an effort to address these concerns, brachytherapy in the form of permanent or temporary implants has been used to deliver high doses to the tumor while effectively sparing the surrounding normal tissue structures [1–9]. Recently, there has been a resurgence of interest in the use of intraoperative radiotherapy (IORT) for pediatric tumors [10–13]. This modality allows for the delivery of a large single dose of radiation to the exposed tumor bed after surgical resection; at the same time normal tissues such as the bowel and other uninvolved organs can be completely shielded or displaced from the irradiated region. As all the treatment is given intraoperatively, prolonged immobilization or sedation, radiation safety, and in-patient nursing care issues relevant for the pediatric patient with a temporary radioactive implant are no longer applicable.

IORT is generally given in the form of electron beam. A potential technical shortcoming of this form of therapy may be related to the relatively bulky nature of the electron cone applicators, which may prevent access to some anatomic locations. As a result, homogeneous dosimetric coverage of target volumes with complex geometric surface contours may not be achieved. At the Memorial Sloan-Kettering Cancer Center, we have developed an intraoperative, flexible, catheter applicator designed to conform to the geometry of the operative bed (Harrison-Anderson-Mick or HAM applicator). This applicator, in turn, is connected to a high-dose-rate remote afterloader, which houses a high activity Iridium source. We have used this form of IORT for various malignancies, including sarcomas, colorectal, thoracic, and gynecologic cancers in the adult patient population [12]. This report presents our preliminary clinical experience with this form of IORT for pediatric tumors.

MATERIALS AND METHODS

A Phase I-II study of high-dose-rate Iridium-192 intraoperative radiotherapy (HDR-IORT) for primary and recurrent solid pediatric tumors was initiated in 1993 at the Memorial Sloan Kettering Cancer Center. The purpose of this study was to determine the feasibility, associated toxicity, and short-term efficacy of HDR-IORT in this group of patients. All eligible patients underwent resection of disease and were evaluated for IORT if residual microscopic or gross tumor was present. Brain and spinal cord tumors were excluded. Only patients <24 years of age were eligible for this study. Patients treated with prior radiation therapy or chemotherapy were not excluded.

All patients underwent surgical exploration and resection in a specially designed operating room shielded for the purpose of HDR-IORT. After resection was performed, the tumor bed was identified and marked with metallic clips. All normal tissue structures, to the extent feasible, were moved out of the field of the tumor bed or shielded with lead discs. The tumor bed was then measured and an appropriately sized intraoperative applicator (Fig. 1) directly placed. The HDR applicator was secured in place with surrounding surgical packing material or in some cases suturing the applicator in place. Once the position of the applicator was optimized, the applicator catheters were attached to the source guide tubes of the high-dose-rate remote afterloader. We developed an atlas for different applicator sizes, which contains predetermined dwell times of the Iridium-192 source within each of the channels of the HAM applicator in order to produce a computer-optimized dose distribution covering the target volume [13]. Calculated dwell times are programmed into the computer, which controls the high-dose-rate remote afterloader. A dose of 1,200 cGy prescribed to a depth of 0.5–1 cm from the surface of the applicator was delivered.

Overall survival, distant metastases-free survival, and local relapse-free survival were calculated from the date of IORT by the Kaplan-Meier product limit method [14]. Subgroup differences in patient characteristics were evaluated by the Chi-square test with Yate's correction [15].

RESULTS

Patient Characteristics

Of the 10 children enrolled on this Phase I-II study, five were male and five were female. The median age at the time of IORT was 15 years (range: 2–18 years). All patients prior to their planned surgery and IORT had persistent (n = 6) or recurrent disease (n = 4) despite standard therapy, which included intensive chemotherapy (n = 7), surgery (n = 5), or external radiotherapy (n = 1). The histology of the treated patients included the following: rhabdomyosarcoma (n = 2), extraosseous Ewing's sarcoma (n = 2), synovial sarcoma (n = 2), Wilms tumor (n = 1), osteosarcoma (n = 1), malignant teratoma (n = 1), and undifferentiated tumor (n = 1). The treated sites included the following: chest wall (n = 3), retroperitoneum (n = 3), pelvis (n = 3), and buttock (n = 1).

Gross total resection was performed in all cases. The margins of resection were microscopically positive in three cases and the remaining patients had close (≤0.5 cm from the resection margin) but negative margins. Due to the recurrent or persistent nature of the disease, the operative bed was considered to be at high risk for residual microscopic disease in all cases and thus mandated further therapy. This was the indication for HDR-IORT in these cases. There were no intraoperative complications. The median estimated blood loss from the entire operative procedure was 400 cc (range 90–1,200 cc). The median postoperative hospital stay was 8.5 days.

The median IORT dose delivered was 1,200 cGy (range: 800–1,500 cGy). The median dimensions of the applicator employed was 7 × 6 cm. The median time to deliver IORT was 18.5 minutes (range: 8–158 min). Five patients were treated with adjunctive postoperative exter-

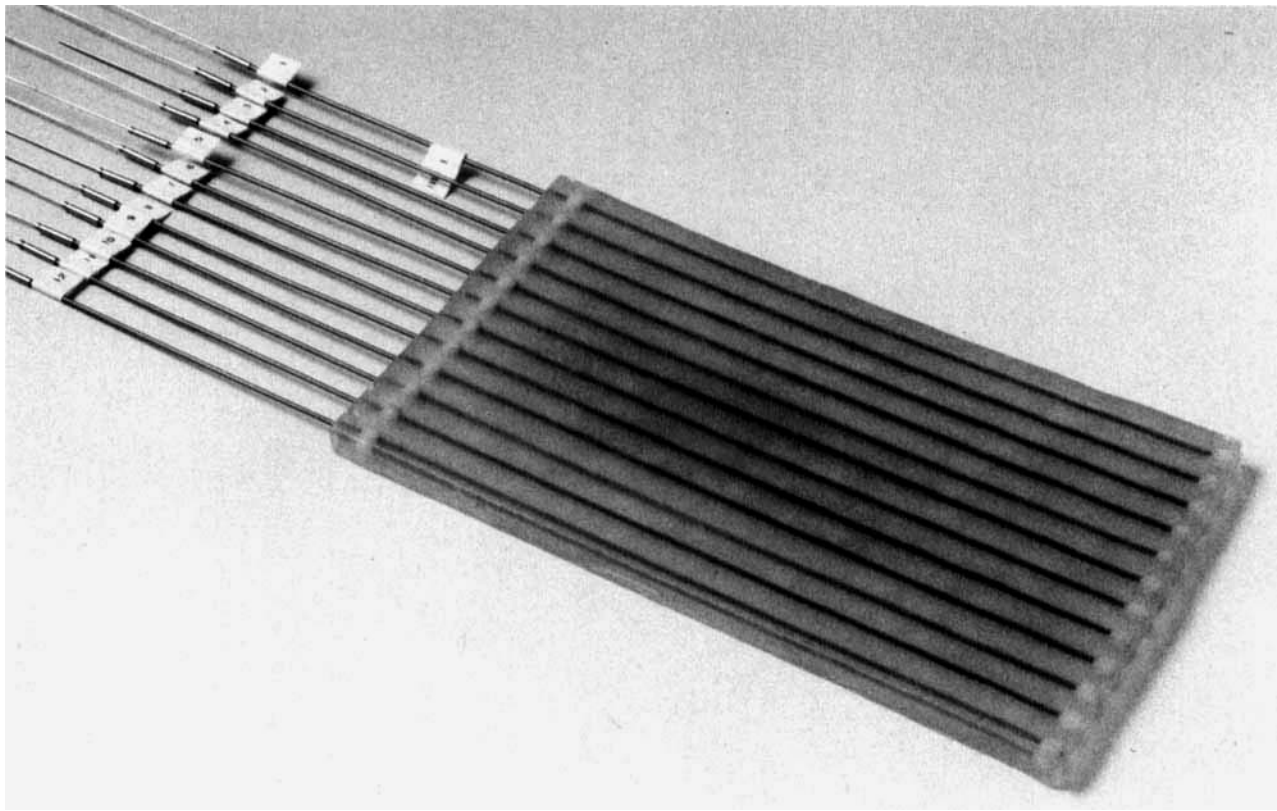

Fig. 1. HAM (Harrison-Anderson-Mick) intraoperative applicator.

nal beam radiotherapy with a median dose of 2,520 cGy (range: 1,000–5,400 cGy). The patient characteristics and treatment information are summarized in Table I.

Treatment-related Complications

One patient with a malignant teratoma arising in the presacral region developed a peri-rectal abscess with fistula formation. In this case, however, surgical manipulation of the rectum was necessary for adequate resection. In addition, as the rectum itself was not felt to be at risk for microscopic disease, it was shielded during the IORT. What role, if any, the IORT played in the development of this complication remains unclear. One patient died of nadir sepsis related to postoperative chemotherapy. No other complications were noted.

Treatment Outcome

Two patients developed recurrence of disease within the treated IORT bed at 4 and 6 months, respectively, after therapy. The 2-year actuarial local-recurrence-free survival is 80% (Fig. 2). Two patients developed distant metastases at 5 and 13 months, respectively, after therapy. One of these patients had a concomitant local failure. The 2-year actuarial distant metastases-free-survival is 59% (Fig. 2). Two patients died of intercurrent disease (one patient with nadir sepsis related to adjuvant chemotherapy and one patient died of a cerebral aneurysm rupture) after therapy but were free of disease at the time of their death. The 1 and 2-year actuarial absolute survival was 64% and 32%, respectively.

DISCUSSION

Our preliminary results demonstrate that HDR-IORT is a safe and effective means of delivering large single doses of radiation for pediatric tumors. Despite the fact that most of the children in this study were heavily pretreated and presented with recurrent or persistent disease, the local control rate at 2 years was 80% and excellent tolerance was noted. Such an approach is especially attractive for this particular patient population for several reasons. First, high doses can be delivered accurately to the directly visualized tumor bed, while normal tissue structures can be effectively displaced or shielded from the irradiated region, thus further enhancing the therapeutic ratio. Furthermore, the ability to deliver the treatment at the time of surgery obviates concerns of sedation and prolonged immobilization, which would be otherwise required for younger children during daily external radio-

TABLE I. Phase I/II Study of IORT for Pediatric Tumors: Summary of Patient Characteristics and Treatment Information

Patient #	Age (years)	Sex	Site	Histology	Previous chemo	Treatment for primary or recurrent	Margin status	IORT[a] dose	Adjuvant therapy[b]	NED and follow-up[c]
1	8	Female	Retroperitoneum	Wilm's tumor	Yes	Recurrent	Negative	12 Gy	XRT 10 Gy and chemo	NED @ 2 years, 2 mos.
2	2	Male	Prostate	Rhabdomyosarcoma	Yes	Primary	Negative	12 Gy	Chemo only	NED @ 2 years
3	18	Female	Sacrum/pelvis	Extraosseous osteosarcoma	Yes	Primary	Positive	15 Gy	Chemo only	Dead of intercurrent disease @ 1 year, 1 month
4	17	Female	Left chest wall	Undifferentiated	Yes	Recurrent	Positive	12 Gy	Chemo only	Dead of persistent disease @ 7 months
5	18	Male	Retroperitoneum	Rhabdomyosarcoma	No	Primary	Negative	12 Gy	XRT 54 Gy and chemo	Distant failure @ 1 year, 1 month DOD @ 1 year, 3 months
6	17	Male	Retroperitoneum	Ewing's sarcoma	Yes	Recurrent	Negative	12 Gy	XRT 15 Gy and chemo	Local and distant failure @ 5 months DOD @ 7 months
7	13	Female	Left chest wall	Monophasic synovial sarcoma	No	Primary	Positive	12 Gy	Chemo only	Local failure @ 4 months DOD @ 5 months
8	8	Female	Pelvis	Teratoma	Yes	Recurrent	Negative	12 Gy	XRT 25.2 Gy	NED @ 11 months
9	18	Male	Buttock	Synovial cell	No	Primary	Negative	18 Gy	XRT 50.4 GY and chemo	NED @ 6 months
10	5	Male	Left chest wall	Ewing's sarcoma	Yes	Primary	Negative	12 Gy	Chemo only	NED @ 5 months

[a] Intraoperative radiation therapy.
[b] XRT = radiation therapy.
[c] NED = no evidence of disease; DOD = dead of disease.

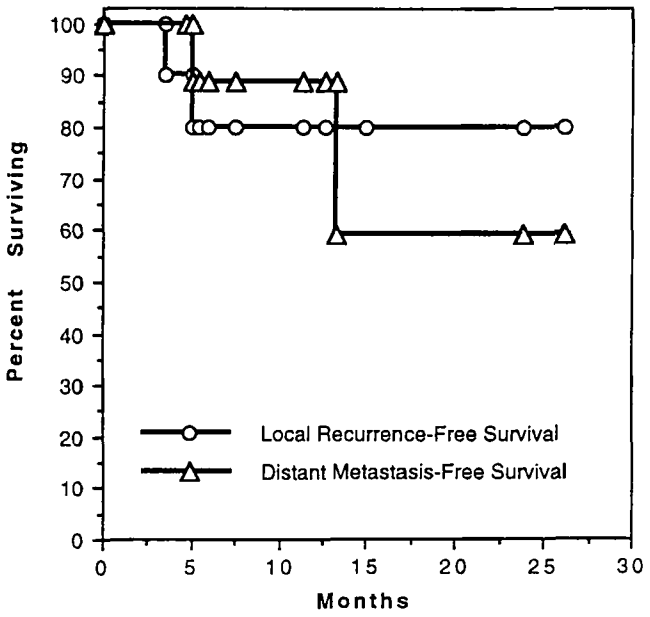

Fig. 2. Actuarial local control and distant metastases-free survival for all patients calculated from the time of intraoperative radiotherapy.

therapy or low-dose-rate brachytherapy. In addition, radiation exposure concerns for the nursing staff and parents are eliminated, thus maintaining the continuous nursing care and interaction between the child, medical staff, and family.

Outcome with pediatric brachytherapy have been previously reported for low-dose-rate systems in the form of temporary or permanent implants [1–8]. Fontanesi et al. [4] recently updated the results of brachytherapy for pediatric tumors at the St. Jude Children's Research Hospital. Forty-three of 50 treated sites have maintained continuous local control with a median follow-up of 39 months. The median time to develop a local failure was 6 months, and no failure developed after 20 months. Serious complications developed in two patients (enterocutaneous fistula in one patient treated with a permanent I-125 implant and a second patient with significant bleeding secondary to catheter removal from the abdominal cavity). Two additional patients developed soft tissue necrosis that responded to conservative measures. Other series [2,5,7,8] have similarly reported excellent local control rates with minimal treatment related complications for pediatric soft tissue sarcomas treated with temporary implants.

Recently, there has been renewed interest in the use of intraoperative radiotherapy for pediatric malignancies. Haase et al. [10] reported results of intraoperative electron beam radiotherapy for advanced pediatric tumors. Treatments were delivered with a dedicated linear accelerator using 5-11 Mev electrons with single doses of 1,000–1,700 cGy to prescribed depths of 0.5–3 cm. Among 48 children with solid tumors including Stage IV neuroblastoma, rhabdomyosarcoma, peripheral neuroepithelial tumors, and Ewing's sarcoma, the local control rate was 75%, with a mean follow-up of 51 months. Treatments were well tolerated with an excellent long-term functional outcome noted. Among 15 surviving children treated at 3 years of age or less, no growth abnormalities were detected with a mean follow-up of 5 years.

There are, however, some potential shortcomings of intraoperative *electron* beam radiotherapy, which may limit its applicability in certain clinical situations. First, the substantial expense required for the allocation of a dedicated linear accelerator in a shielded operating room limits the availability of this modality to selected large tertiary cancer centers. Second, given the inflexible nature of electron cones, steeply sloping surfaces or narrow cavities particularly in the pelvis, retroperitoneum, or thoracic cavity may be technically difficult to encompass.

To address these considerations, several institutions including our own have developed a method to deliver intraoperative, high-dose-rate remote brachytherapy. The remote afterloader is mobile and transportable, thus obviating the expense associated with a dedicated linear accelerator limited to a particular operating room. With our facility design, the entire surgical and brachytherapy procedure is performed in the same room, eliminating the intraoperative transport issues that other IORT techniques require. Dose distributions of the HAM applicator used with this modality conform more easily to the complex geometric surface contours often present for pelvic or retroperitoneal tumors. It should be noted that for situations of residual disease with tumor thickness > 1 cm, dose distributions may be suboptimal. In these cases, we have generally added a permanent I-125 implant (12) to supplement the dose to the gross disease. Higher energy electron IORT may be more advantageous in this setting, eliminating the need for a permanent implant in the pediatric patient.

Nag [9] has reported the preliminary results of high-dose-rate remote brachytherapy among seven previously untreated children with group III rhabdomyosarcoma. The high-dose-rate therapy was part of a multimodality program that included organ-sparing surgery, aggressive chemotherapy, and brachytherapy. The age of the treated children ranged from 6–36 months. In these patients, single or multiplane interstitial implantation was performed and the minimum peripheral dose was 36 Gy in 12 treatments over 8 elapsed days. With a median follow-up of 26 months, all patients are alive without evidence of disease and with excellent tolerance of this treatment program.

The implications of HDR-IORT and the potential of impact in the management of pediatric malignancies are clearly far-reaching. There has always been justifiable concern utilizing radiotherapy in the growing child. The potential late effects on bone growth, overall develop-

mental function, fertility, and induction of second malignancies are important considerations. Many studies have corroborated the enhancement of local control and disease-free survival with the addition of radiotherapy to systemic therapy for several pediatric solid tumors [16,17]. Treatment modalities such as IORT facilitates the delivery of higher doses of radiation with the ability to exclude the surrounding growing normal tissue from the high dose region. Frequently, IORT is used in combination with external beam radiotherapy to extract the radiobiological benefits of fractionated treatment. For pediatric tumors, modest doses of external beam radiotherapy may be sufficient to control microscopic disease if combined with intraoperative boost therapy. Future studies will be necessary to define the role of IORT and the optimal combination regimen with external beam radiotherapy that would provide the best functional outcome without compromise of local control and disease-free survival.

CONCLUSIONS

Intraoperative high-dose-rate radiation is a safe and well-tolerated means of delivering large doses of radiation for pediatric solid tumors. In this phase I/II study, the 2-year actuarial local control rate was 80% and the 2-year incidence of distant metastases was 41%. Longer follow-up will be needed to fully assess the toxicity and efficacy of this approach.

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